

1 **Pregnancy and breastfeeding during COVID-19 pandemic: A systematic review of**  
2 **published pregnancy cases**

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26 **Abstract**

27 **Background:** The COVID-19 pandemic is an emerging concern regarding the potential  
28 adverse effects during pregnancy. This study reviews knowledge on the impact of  
29 COVID-19 on pregnancy and describes the outcome of published cases of pregnant  
30 women diagnosed with COVID-19.

31 **Methods:** Searches were conducted in PubMed® up to 8 April 2020, using PRISMA  
32 standards, to identify original published studies describing pregnant women at any  
33 gestational age diagnosed COVID-19. There were no date or language restrictions on the  
34 search. All identified studies were included irrespective of assumptions on study quality.

35 **Results:** We identified 30 original studies reporting 212 cases of pregnant women with  
36 COVID-19 (30 discharged while pregnant), 200 from China and 12 from other countries.  
37 The 182 published deliveries resulted in one stillbirth and 185 live births. Four women  
38 with severe COVID-19 required admission to an intensive care unit but no cases of  
39 maternal death were reported. There was one neonatal death. Preterm births occurred in  
40 28.7% of cases, but it is unclear whether this was iatrogenic. All cases with amniotic fluid,  
41 placenta, and/or cord blood analyzed for the SARS-CoV-2 virus were negative. Four  
42 newborns were positive for SARS-CoV-2 and three newborns had high levels of IgM  
43 antibodies. Breast milk samples from 13 mothers and described in seven studies showed  
44 no evidence of SARS-CoV-2.

45 **Conclusion:** The evidence related to the effect of COVID-19 on pregnant women is still  
46 limited. Pregnant women and newborns should be considered particularly vulnerable  
47 populations regarding COVID-19 prevention and management strategies.

48

49 **Keywords:** COVID-19, SARS-COV-2, Pregnancy, Vertical transmission, Breastfeeding,  
50 Perinatal outcomes, systematic review.

## 51 **Introduction**

52 The disease resulting from infection with the Severe Acute Respiratory Syndrome  
53 Coronavirus 2 (SARS-COV-2) and designated COVID-19 by the World Health  
54 Organization (WHO) was first identified in humans in December 2019, in the city of  
55 Wuhan, China,<sup>1</sup> and can present from asymptomatic to a severe acute respiratory infection  
56 requiring intensive care.<sup>2, 3</sup> The infection can occur at any age, but COVID-19 is  
57 proportionally uncommon in children (<1% of the total cases). The infection fatality rate  
58 is around 1% but much higher in older people or those with pre-existing medical  
59 conditions (such as heart disease, diabetes, COPD).<sup>2, 4</sup>

60 Person-to-person transmission of COVID-19 is well established and can occur when an  
61 infected person coughs, sneezes or speaks and scattered droplets are inhaled or reach the  
62 mucous membranes of the mouth, nose or eyes of susceptible. COVID-19 can also be  
63 transmitted through direct hand contact with surfaces or objects contaminated with  
64 SARS-CoV-2 followed by contact with the mouth, nose or eyes.<sup>2</sup>

65 Pregnant women and newborns receive special attention and there is an emerging concern  
66 with the potential risk of SARS-COV-2 vertical transmission (from mother to fetus) or  
67 associated malformations, and contagion during delivery and breastfeeding; likewise, it  
68 is important to determine the potential adverse effects of COVID-19 in pregnant women.<sup>5-</sup>

69 <sup>8</sup> However, in general, the available information remains scarce.

70 This study reviews published cases of pregnant women diagnosed with COVID-19.

71

## 72 **Methods**

73 The review follows the Preferred Reporting of Systematic Reviews and Meta-Analysis  
74 (PRISMA) guidelines.<sup>9, 10</sup>

75 We searched PubMed® up to 8 April 2020 to identify original published studies  
76 describing pregnant women at any gestational age diagnosed with COVID-19 (confirmed  
77 by clinical/radiological evidence of pneumonia compatible with SARS-CoV-2 and/or by  
78 quantitative real-time polymerase chain reaction (PCR) or dual fluorescence PCR of  
79 SARS-CoV-2 infection). The following search expression was used [(COVID-19 OR  
80 2019-nCoV OR "novel coronavirus" OR SARS-CoV-2 OR "coronavirus 2") AND  
81 (pregnancy OR delivery OR pregnant OR obstetric\* OR maternal OR perinatal OR  
82 breastfeeding)]. Also, reference tracking was carried out to identify other potential studies  
83 to be included.

84 Each reference retrieved was screened independently by two researchers (IB and RD)  
85 following predefined criteria to determine eligibility for the systematic review. Studies  
86 were excluded if: (1) did not involve humans (e.g. in vitro or animal research); (2) non-  
87 original articles (e.g. book chapters, review articles, editorials, comments, guidelines); (3)  
88 data not reporting pregnant women diagnosed with COVID-19; and (4) duplicate studies  
89 or evaluating the same sample. There were no date or language restrictions on the search.

90 Two researchers (IB and RD) reviewed the included studies and extracted the following  
91 data: collection period, maternal age, pregnancy complications, type of delivery,  
92 indication for cesarean section, gestational age at birth (or at admission), pregnancy  
93 outcome, maternal admission to intensive care unit, maternal death, neonatal outcomes  
94 (birth weight, Apgar at 1 and 5 minutes, neonatal complications, breastfeeding),  
95 intrauterine and/or neonatal samples collected for detection of SARS-CoV-2 (such as  
96 amniotic fluid, cord blood, placenta, breast milk, nasopharyngeal and anal swabs) and  
97 their results (negative/positive).

98 All identified original studies reporting cases of pregnant women at any gestational age  
99 diagnosed with COVID-19 were included irrespective of study quality. Cases reported in

100 more than one study, and for which it was possible to identify duplicates, were described  
101 only once, presenting the more detailed data. We identified duplicates based on author  
102 names and hospital location, publication date, participant admission date, maternal and  
103 neonatal characteristics and outcomes.

104 Doubts on possible duplicates and/or differences in the data extraction were discussed  
105 and resolved by consensus, involving a third researcher (CR) whenever necessary.

106

107

## 112 **Results**

113 Table 1 summarizes the main characteristics of the 212 reported cases of pregnant women  
114 diagnosed with COVID-19 and identified in 30 original studies published until April 8,  
115 2020. A detailed description of each reported case is presented in Table S1 (supplemental  
116 material).

117 All published cases occurred in China, except eight from the United States of America,<sup>11</sup>,  
118 <sup>12</sup> one from South Korea,<sup>13</sup> one from Honduras,<sup>14</sup> one from Turkey,<sup>15</sup> and another from  
119 Sweden.<sup>16</sup> Maternal age ranged from 22 to 41 years. From the 212 pregnant women  
120 described, 182 delivered and 30 were discharged during pregnancy (undelivered). Most  
121 women were in the third trimester of pregnancy and there was only one study reporting  
122 pregnant women in the first trimester.<sup>17</sup>

123

### 124 **Vertical transmission of COVID-19**

125 All cases in which amniotic fluid, placenta, and/or cord blood were analyzed for SARS-  
126 CoV-2 virus were negative.<sup>5, 11, 13, 15, 18-26</sup>

127 Most studies detected the SARS-CoV-2 RNA by real-time reverse transcription-  
128 polymerase chain reaction (RT-PCR) using samples from the newborn's nasopharyngeal

129 or throat, sample collection varying from immediately to 9 days after birth. Two studies  
130 also used maternal and neonatal sera samples to test for IgG and IgM antibodies.<sup>27, 28</sup>  
131 Four newborns (2.2%) presented positive oral swabs for SARS-CoV-2.<sup>21, 24, 25, 29</sup> In a  
132 cohort of 33 newborns from mothers with COVID-19, admitted to the Pediatric Hospital  
133 of Wuhan, three of the newborns had positive RT-PCR for SARS-CoV-2 in  
134 nasopharyngeal and anal swabs collected on the second and fourth days after delivery,  
135 with negative results on the sixth day for two newborns and on the seventh day for  
136 another. However, placenta, amniotic fluid, and cord blood samples were not analyzed.<sup>29</sup>  
137 There is yet another case of a newborn with a positive RT-PCR for SARS COV-2 in one  
138 throat swab collected at 36 hours after birth.<sup>21, 24</sup> However, it was not possible to confirm  
139 whether it was a real case of intrauterine transmission since the umbilical cord and  
140 placenta blood samples were negative for SARS-CoV-2 and the possibility of postnatal  
141 contact could not be discarded.<sup>21, 24</sup> No other study reported positive results for the SARS-  
142 CoV-2 virus in nasopharyngeal exudates from newborns of mothers diagnosed with  
143 COVID-19.<sup>5, 11-20, 22-26, 29-36</sup>  
144 In a series of six cases that had blood collected after delivery evaluated, two of the  
145 newborns had high levels of IgG and IgM antibodies (>10 AU/mL) and three had high  
146 values of IgG antibodies with normal levels of IgM in, but in none SARS-CoV-2 virus  
147 was detected by RT-PCR in the oropharyngeal exudate.<sup>27</sup> A case study also reported high  
148 values of IgM and IgG antibodies in the blood at days 1 and 15 after delivery, but with  
149 RT-PCR for SARS-CoV-2 negative in five samples of nasopharyngeal exudates collected  
150 between the first two hours and the 16<sup>th</sup> day of life.<sup>28</sup>  
151 Seven studies reported the test of breast milk samples from 13 mothers and none  
152 evidenced SARS-CoV-2 virus.<sup>5, 15, 16, 20-22, 28</sup>

153

154 **Maternal and neonatal outcomes**

155 The clinical and obstetric conditions most frequently reported were fetal distress (n=20),  
156 gestational diabetes (n=13), gestational hypertension (n=11), premature rupture of  
157 membranes (PROM) (n=7), anemia (n=5), placenta previa/bleeding in the third trimester  
158 (n=5), pre-eclampsia (n=4), hypothyroidism (n=4), chronic hypertension (n=3),  
159 thalassemia(n=2), polycystic ovary syndrome (n=2), cholecystitis (n=2), asthma (n=2),  
160 diabetes mellitus type 2 (n=2), placental abruption (n=1), oligohydramnios(n=1),  
161 polyhydramnios (n=1), hepatitis B infection (n=1) and mitral valve and tricuspid valve  
162 replacement (n=1). In one study that compared groups of pregnant women with and  
163 without COVID-19, there were no significant differences in the occurrence of gestational  
164 diabetes, severe pre-eclampsia, PROM, fetal distress, meconium-stained amniotic fluid,  
165 premature delivery, neonatal asphyxia and procedures for severe post-partum bleeding.<sup>30</sup>  
166 Cesarean section was the most common type of delivery: 88.0% of 158 cases with  
167 available information. Most studies did not specify the indication for the cesarean section.  
168 Four pregnant women with severe COVID-19 required admission to an intensive care  
169 unit: one at 30 weeks of gestation, after an emergency cesarean section;<sup>19</sup> another case at  
170 34 weeks of gestation that resulted in an emergency cesarean for a stillbirth;<sup>31</sup> and other  
171 two cases at 37 weeks of gestation of women with high BMI (>35) and history of medical  
172 complications, admitted for labor induction.<sup>12</sup> No maternal deaths from COVID-19 were  
173 published.

174 The 182 deliveries resulted in one stillbirth (intrauterine fetal death)<sup>31</sup> and 185 live births  
175 (four twin pregnancies). There was one neonatal death in a preterm infant (34 completed  
176 weeks of gestation) from a pregnant woman with vaginal bleeding in the third trimester.<sup>18</sup>  
177 Preterm birth occurred in 28.7% (45/157) among those with available information on  
178 gestational age. Approximately 16% of preterm births were spontaneous due to PROM<sup>5</sup>.

179 18, 29, 31, 36 or spontaneous onset of labor,<sup>14</sup> but in most cases, it is unclear whether these  
180 were spontaneous or iatrogenic.

181 Although all breast milk samples from COVID-19 infected mothers have tested negative  
182 for the SARS-CoV-2 virus, most infants did not receive breast milk.

183

## 184 **Discussion**

185 There is no evidence that the risk of infection with COVID-19 in pregnant women is  
186 greater than in the general population.<sup>7, 37</sup> However, the incidence of infection in pregnant  
187 women is unknown, as screening tests were not generally used, except in the presence of  
188 symptoms. In a New York's hospital that implemented universal SARS-CoV-2 testing in  
189 all pregnant women admitted for delivery, 15.4% of them were positive for SARS-CoV-  
190 2, but 87.9% were asymptomatic.<sup>38</sup>

191 Although most of the published cases confirm the absence of transmission of the SARS-  
192 CoV-2 virus antenatally or intrapartum, at least when the infection occurs in the third  
193 trimester of pregnancy,<sup>5, 11, 13, 15, 18-26</sup> emerging evidence has suggested that vertical  
194 transmission is possible.<sup>21, 24, 25, 27-29</sup> However, the evidence is still limited to a reduced  
195 number of reported cases, large variability in the type of biological material analyzed and  
196 the time of its collection. Even if vertical transmission occurred in the reported cases, the  
197 proportion would be low, below 5% of the published cases.

198 Regarding the effect of the SARS-CoV-2 virus on the fetus, no congenital malformation  
199 has been reported so far and the association of COVID-19 and fetal malformation seems  
200 unlikely considering the reduced risk of intrauterine infection.<sup>37</sup>

201 Higher risk of fetal distress and preterm births have been reported, but it is unclear if  
202 preterm birth occurs spontaneously (spontaneous onset of labor or following PROM) or  
203 is iatrogenic. The evidence related to the effect of COVID-19 on pregnant women is still



204 limited. The clinical characteristics of COVID-19 were similar to those described in non-  
205 pregnant women, suggesting that the prognosis is not worse in pregnant women, although  
206 the number of cases studied is still reduced.<sup>5, 18, 31-34</sup> A recent systematic review  
207 summarized the clinical manifestations of 108 pregnant women confirmed with COVID-  
208 19 and most of them presented fever (68%) and coughing (34%), and lymphocytopenia  
209 (59%) with elevated C-reactive protein (70%).<sup>39</sup>

210 The maternal and neonatal outcomes observed so far are quite different from the two most  
211 serious coronavirus-related previous epidemics.<sup>7, 40-53</sup> The first also appeared in China, in  
212 2002-03, and was characterized by severe respiratory infections caused by the Severe  
213 Acute Respiratory Syndrome-Coronavirus (SARS-CoV). The second occurred in 2012,  
214 initially in the Middle East, the Middle East Respiratory Syndrome - Coronavirus  
215 (MERS-CoV).<sup>7, 40</sup> These epidemics have demonstrated the ability of coronavirus to cause  
216 serious complications during pregnancy,<sup>43, 53</sup> with worse prognosis in pregnant women  
217 than non-pregnant women.<sup>42, 54</sup>

218 In the 2002 epidemic, 12 pregnant women were infected with SARS-CoV, with a fatality  
219 rate of 25%.<sup>53</sup> Among the seven pregnant women infected in the first trimester, four had  
220 a miscarriage.<sup>53</sup> Two of the five pregnant women infected during the second or third  
221 trimester had fetal growth restriction and four had a preterm delivery (one spontaneous;  
222 three induced by the maternal condition).<sup>53</sup> In a review of the pregnancy outcomes of 11  
223 women infected with MERS-CoV, seven pregnant women required admission to the  
224 intensive care unit and three died, of which only one had one comorbidity (asthma). Two  
225 fetal deaths occurred, and three of nine newborns were preterm.<sup>43</sup>

226 However, considering that SARS-CoV-2 has genetic homology and some clinical  
227 similarities to SARS-CoV and MERS-CoV, and the immunological and physiological  
228 changes that occur during pregnancy, such as in cell-mediated immunity or lung function,

229 that affect both the susceptibility and the clinical severity of pneumonia, it is important  
230 to pay particular attention to the monitoring of pregnant women with COVID-19, because  
231 maternal and perinatal adverse outcomes are potentially relevant.<sup>7, 40</sup> Although there were  
232 no maternal deaths described, possible maternal deaths were reported in social media, but  
233 without any robust evidence.<sup>37</sup> Furthermore, one study reported two asymptomatic  
234 pregnant women at admission for delivery that rapidly evolved to severe COVID-19  
235 disease requiring admission to an intensive care unit.<sup>12</sup>

236 Thus, it is essential to prevent the infection of COVID-19 and any other viral respiratory  
237 infection, as these infections represent an increased risk for the pregnant woman and for  
238 the pregnancy itself.<sup>7, 55, 56</sup> It is therefore extremely important that pregnant women adopt  
239 preventive actions for COVID-19 with great intensity.<sup>37</sup> For pregnant women with  
240 suspected or confirmed infection with SARS-CoV-2, recommendations for health  
241 professionals and services have already been published.<sup>37, 55, 57-59</sup>

242 Most women in this review had a cesarean section, many of them without a clear medical  
243 indication. The decision on the type of delivery in pregnant women with suspected or  
244 confirmed infection with COVID-19 should take into account the maternal and fetal  
245 clinical characteristics, as in normal practice, and not the diagnosis of COVID-19  
246 infection per se. Thus, there is no obstetric contraindication to any mode of delivery,  
247 unless the pregnant woman's clinical condition implies an emergent decision.<sup>37</sup>

248 In Portugal, we can estimate that about 80,000 pregnant women are exposed to the  
249 pandemic at different gestational ages, which represents an important challenge for  
250 individual and public health, to avoid infection in this population that should be  
251 considered at higher risk. According to the information reported by health professionals,  
252 there were eight cases of COVID-19 positive women delivered in Portugal by the 31st of  
253 March 2020. None of the first eight infants (all live births) born in Portugal tested positive

254 for the SARS-CoV-2. Preterm birth occurred in 25% (2/8) of them and 5 (62.5%) resulted  
255 in cesarean section.

256 The limited scientific knowledge currently available makes it difficult to develop specific  
257 breastfeeding recommendations. There is not enough scientific evidence to unequivocally  
258 state that there is no possibility that mothers with COVID-19 can transmit the virus  
259 through breast milk.<sup>55</sup> Therefore, recommendations should be based on the available data  
260 <sup>5, 15, 16, 20-22, 28</sup> and the analogy with past circumstances and predictable costs and benefits.

261 Breastfeeding is recognized as the best form of child feeding due to the countless benefits  
262 for both the mother and the newborn, including the protection against gastrointestinal and  
263 respiratory infections.<sup>60</sup> Thus, considering the benefits of breastfeeding and the fact that  
264 the transmission of other respiratory viruses is insignificant through breast milk, there is  
265 no indication to stop breastfeeding. According to the recommendations of  
266 WHO/UNICEF<sup>61</sup> and the Center for Disease Control and Prevention (CDC) of the United  
267 States,<sup>55</sup> women with suspected or confirmed infection with COVID-19 can initiate or  
268 continue breastfeeding as long as clinical conditions permit. The CDC indicates that the  
269 decision to initiate or continue breastfeeding must be determined by the mother with  
270 COVID-19, together with family members and health professionals.<sup>55</sup>

271 Limitations of this systematic review should be acknowledged. Considerable  
272 heterogeneity was observed across the studies, which did not allow us to conduct a meta-  
273 analysis. On the other hand, we cannot guarantee that we were able to identify all the  
274 cases of pregnant women described in the literature. Possibly there are additional cases  
275 currently presented in other types of publications, such as reports. Also, considering the  
276 importance of summarizing all existing cases, we did not assess the quality of the studies  
277 included in this review. Several studies had missing outcome data and selective reporting  
278 bias could not be excluded. Additionally, there may be some cases which could be

279 duplicated, namely the studies which did not describe clinical characteristics case by  
280 case.<sup>30, 33, 34, 36</sup>

281

## 282 **Conclusion**

283 According to this review, fetal distress and preterm delivery seem to be more frequent  
284 among pregnant women with COVID-19. There is emerging evidence on possible vertical  
285 transmission (four positive results in the neonatal oral swabs for SARS-CoV-2 were  
286 reported and three newborns had high values of IgM antibodies), but the clinical relevance  
287 of the fetal infection is unclear. So far, there is no evidence that the SARS-CoV-2 virus  
288 is transmitted through breast milk. Maternal deaths were not reported and hospitalizations  
289 in intensive care were uncommon. Although the complications appear to be similar to  
290 those of non-pregnant women, services must be prepared to attend to complications,  
291 especially in pregnant women with comorbidities. Therefore, pregnant women and  
292 newborns should be considered particularly vulnerable populations regarding COVID-19  
293 prevention and management strategies. Information, counseling and adequate monitoring  
294 are essential to prevent major adverse effects of SARS-CoV-2 infection during  
295 pregnancy.

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317

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320

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329

330 **Ethics approval**

331 This study is a systematic review based on published studies; therefore, ethical approval  
332 was not required.

333

334 **Authors' contributions**

- 335 Carina Rodrigues and Henrique Barros: Conceptualization, Original draft preparation.
- 336 Inês Baía and Rosa Domingues: Methodology, Data curation, Writing-Reviewing, and
- 337 Editing. All authors read and approved the final manuscript.

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511 **Table 1. Characteristics of pregnant women diagnosed with COVID-19 described in**  
 512 **the literature (n=212).**

513

|  | n/N (%)        |
|--|----------------|
| <b>Maternal characteristics</b>              |                |
| Age, years (min-max)                         | 22-43          |
| Country of hospital admission                |                |
| China  | 200/212 (94.3) |
| United States of America                     | 8/212 (3.8)    |
| South Korea                                  | 1/212 (0.5)    |
| Honduras                                     | 1/212 (0.5)    |
| Turkey                                       | 1/212 (0.5)    |
| Sweden                                       | 1/212 (0.5)    |
| <b>Pregnancy complications</b>               |                |
| Fetal distress                               | 20/212 (9.4)   |
| Gestational diabetes                         | 13/212 (6.1)   |
| Gestational hypertension                     | 11/212 (5.2)   |
| PROM   | 7/212 (3.3)    |
| Anemia                                       | 5/212 (2.4)    |
| Placenta previa/bleeding                     | 5/212 (2.4)    |
| Preeclampsia                                 | 4/212 (1.9)    |
| Hypothyroidism                               | 4/212 (1.9)    |
| Chronic hypertension                         | 3/212 (1.4)    |
| Thalassemia                                  | 2/212 (0.9)    |
| Polycystic ovary syndrome                    | 2/212 (0.9)    |
| Cholecystitis                                | 2/212 (0.9)    |
| Asthma                                       | 2/212 (0.9)    |
| Diabetes mellitus type 2                     | 2/212 (0.9)    |
| Placental abruption                          | 1/212 (0.5)    |
| Oligohydramnios                              | 1/212 (0.5)    |
| Polyhydramnios                               | 1/212 (0.5)    |
| Hepatitis B infection                        | 1/212 (0.5)    |
| Mitral valve and tricuspid valve replacement | 1/212 (0.5)    |
| <b>Pregnancy characteristics/outcomes</b>    |                |
| Pregnant women at discharge (undelivered)    | 30/212 (14.2)  |
| Multiple pregnancies                         | 4/212 (1.9)    |
| Deliveries                                   | 182/212 (85.8) |
| Multiple pregnancies delivered               | 4/182 (2.2)    |
| Stillbirths                                  | 1/186 (0.5)    |

|   |                |
|---|----------------|
| Live births   | 185/186 (99.5) |
| Cesarean section  | 139/158 (88.0) |
| Preterm birth (<37 weeks of gestation)                              | 45/157 (28.7)  |
| <b>Maternal outcomes</b>  |                |
| Maternal deaths   | 0/212 (0.0)    |
| Maternal admission to Intensive Care Unit                           | 4/212 (1.9)    |
| <b>Neonatal outcomes</b>  |                |
| Neonatal deaths   | 1/185 (0.5)    |
| SARS-CoV-2 infection confirmed by oral swabs                        | 4/185 (2.2)    |
| High levels of SARS-CoV-2 IgM antibodies                            | 3/185 (1.6)    |
| <b>Type of intrauterine/ neonatal samples collected and results</b> |                |
| Placenta  | 21/186 (11.3)  |
| Positive results  | 0/21 (0.0)     |
| Cord blood  | 13/186 (7.0)   |
| Positive results  | 0/13 (0.0)     |
| Amniotic fluid  | 14/186 (7.5)   |
| Positive results  | 0/14 (0.0)     |
| Newborn's oral swabs  | 70/185 (33.8)  |
| Positive results  | 4/70 (5.7)     |
| Measurement of SARS-CoV-2 IgM and IgG antibody                      | 7/185 (3.8)    |
| Reactive IgM  | 3/7 (42.8)     |
| Reactive IgG  | 6/7 (85.7)     |
| Breast milk   | 13/185 (7.0)   |
| Positive results  | 0/13 (0.0)     |

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